REMARKS

Claim Amendments

Claims 94–120 are pending in the Application. Claims 95, 97, 99, 101, 102, 103, 105, 107, 108, 109, 111, 118 and 119 have been newly cancelled by Applicant. Claims 94, 96, 98, 100, 104, 106, 110, 112, 113, 114, 115, 116, 117 and 120 have been newly amended. Support for the claim amendments is found throughout the specification and in the originally filed claims. No new matter has been added.

Claims 94, 96 and 98 have been amended so as to recite a method of classifying a human test subject as more likely to have schizophrenia than to be healthy if the level of RNA encoded by BTG2 in blood of the test subject is higher with a fold change of 2.49 relative to healthy subjects.

Specification support for claiming a method of classifying a human test subject as more likely to have schizophrenia than to be healthy can be found, for example, at paragraphs [0134] and [0135] of the published application (Pub. No.: US 2004/0241727 Al), which describe characterization of an unknown sample (i.e. of a test subject of unknown disease-related status) as having a disease or not via class prediction, and which provides ample prior art literature guidance for practicing such class prediction, in accordance with these claims.

Claims rejections – 35 USC § 112 1st paragraph, Written Description

Claims 94–117 and 120 are rejected under 35 USC § 112 1st paragraph, written description. Applicant respectfully traverses. Claims 95, 97, 99, 101, 102, 103, 105, 107, 108, 109, 111, 118 and 119 have been newly canceled by Applicant. Claims 94, 96, 98, 100, 104, 106, 110, 112, 113, 114, 115, 116, 117 and 120 have been newly amended.

The Office Action contends that the response does not identify basis for recitation in the claims of limitations wherein the expression is higher or lower "with a fold change of at least 2" or wherein the fold change is at least 2.5.

In ordert to expedite prosecution, Applicant has amended claims 94, 96, 98, 100, 104, 106, and 110 so as to replace the limitation of a fold change of at least "2" with the limitation of

a fold change of at least "2.49", and has canceled claims 95, 97, 99, 101, 102, 103, 105, 107, 108, 109, 111, 118 and 119.

In view of the remarks and claim amendments, Applicant respectfully requests reconsideration and withdrawal of the rejection of the instant claims.

Claims rejections – 35 USC § 112 1st paragraph, enablement

Claims 94–120 are rejected under 35 U.S.C § 112 1st paragraph, enablement. Applicant respectfully traverses. Claims 95, 97, 99, 101, 102, 103, 105, 107, 108, 109, 111, 118 and 119 have been newly cancelled by Applicant. Claims 94, 96, 98, 100, 104, 106, 110, 112, 113, 114, 115, 116, 117 and 120 have been newly amended.

Applicant respectfully disagrees with the rejection's assertion that the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention in view of the breadth of the claims, the amount of guidance provided by the specification, and the level of predictability in the art.

Applicant submits that the invention is taught in such terms that the claims are to be considered formally enabled, even if only to a minimal extent, particularly in the case of claims merely relating to classifying a human test subject for being a candidate for having schizophrenia, which only require a minimal level of increased probability for such classification. Nevertheless in order to expedite prosecution of the application while more clearly setting forth the claimed subject matter, Applicant has amended claims 94, 96 and 98 so as to recite a method for simply classifying a human test subject as more likely to have schizophrenia than to be healthy.

Applicant has identified the gene BTG2 as more highly expressed with an average fold change of 2.49 in individuals diagnosed as having schizophrenia relative to healthy controls by demonstrating a statistically higher level of RNA. The statistical significance of the differential expression of BTG2 among the experimental subjects tested is evidenced by its p value of 0.0076, as listed in Example 27 (Table 3Y). Applicant respectfully submits that it inherently follows that, in the absence of contradictory information, the gene expression data disclosed is to be presumed to be informative to a given extent so as to formally enable the claims to at least a

minimal and sufficient extent, if only for patenting purposes, regardless of the number of experimental subjects on which the data is based, and regardless of the extent of the classification power conferred by the data beyond the minimum necessary to satisfy the plain language requirements of the claims. Applicant respectfully submits that it inherently follows that the disclosed data is presumed to be statistically informative to formally enable, in particular, claims 94, 96 and 98, which relate to a method of simply classifying a test subject as more likely to have schizophrenia than to be healthy. Based on the disclosed data, and absent contradictory data, claims 94, 96 and 98, in particular, are to be considered to be formally enabled, if only to a minimal extent, even if they were to be hypothetically considered to enable classifying a test subject as only minimally more likely to have schizophrenia than to be healthy, which would be sufficient to satisfy at least the minimal plain language requirements of these claims.

Applicant respectfully submits that in the highly complex field of schizophrenia diagnostics, in which there is a long-felt need for objective means of diagnosis, any method which can facilitate diagnosis, even to a minimal extent, has specific and substantial utility. This is clearly evidenced by the prior art literature which teaches that schizophrenia is "*extraordinarily complex*", that "*heterogeneity in the clinical presentation of schizophrenia is certain*" (refer, for example, to the enclosed prior art Abstract of: Andreasen NC, Carpenter WT Jr., 1993. Diagnosis and classification of schizophrenia. Schizophr Bull. 19:199). This is further very clearly evidenced by the recent post-filing art literature which acknowledges that "*Schizophrenia is a complex neuropsychiatric disease but, despite extensive research efforts over the last 100 years, the etiology of this disorder remains elusive. Diagnosis is still based on a subjective, interview-based process, which may not align with the biological underpinnings of the symptoms.*", that "*there is an urgent need to discover biochemical analytes that facilitate an objective and reliable diagnosis*", and that "*Although numerous studies have aimed to identify potential diagnostic markers in the CSF of schizophrenia patients, as yet not one has found its way to clinical application.*" (see enclosed Abstract of: Schwarz E, Bahn S., 2008. Expert Rev Mol Diagn. 8:209).

In view of the remarks and claim amendments, Applicant respectfully requests reconsideration and withdrawal of the rejection of the instant claims.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. No new matter is added. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

A petition for extension of time is attached. However, should any fees be required to ensure consideration of this response, the Commissioner is authorized to charge Deposit Account 04-1105, Reference No. 2055P(204231).

Respectfully submitted,

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Abstract of: Andreasen NC, Carpenter WT Jr., 1993. Diagnosis and classification of schizophrenia. Schizophr Bull. 19:199; and

Abstract of: Schwarz E, Bahn S., 2008. Expert Rev Mol Diagn. 8:209.

Andreasen NC, Carpenter WT Jr., 1993. Diagnosis and classification of schizophrenia. Schizophr Bull. 19:199

Schizophrenia is a clinical syndrome of both extraordinary importance and extraordinary complexity. Its conceptual history contains many perspectives on the "essential" nature of the illness. For example, Kraepelin in 1919 emphasized primarily onset and course, although he also stressed the importance of some symptoms such as changes in affect and volition. Bleuler in 1911 took a more cross-sectional approach and attempted to identify fundamental characteristic symptoms, especially stressing fragmenting of thought processes. Schneider's (1959) approach was cross-sectional, stressing a group of "first-rank symptoms." DSM-III and its successors attempted to achieve a synthesis of these concepts. Nevertheless, heterogeneity in the clinical presentation of schizophrenia is certain, and heterogeneity in pathophysiology and etiology is likely. Although we can now define a particular construct of schizophrenia with reasonable agreement, the construct must be recognized as provisional and based on a need to achieve consensus about definitions rather than on an understanding of pathophysiology and etiology. The major challenge confronting the student of schizophrenia is to identify its mechanisms and causes in order to develop improved strategies for treatment and prevention. Several different approaches have been proposed to achieve this goal. Early attempts to explore and validate the construct of schizophrenia stressed descriptive and epidemiological techniques; the "validity" of a given construct of schizophrenia would be determined by evaluation of familial aggregation, course and outcome, response to treatment, and laboratory tests. This earlier approach to validation is now complemented by one that draws on techniques from neuroscience and attempts to understand schizophrenia in terms of underlying neural mechanisms. While the earlier approach conceptualized schizophrenia primarily in terms of a single disease entity, the second approach is particularly useful for the exploration of subtypes or dimensions. Research strategies for the study of schizophrenia have been developed to explore its heterogeneity. Three different competing models are discussed: (1) A single etiopathological process leading to diverse manifestations, similar to multiple sclerosis; (2) multiple disease entities leading to schizophrenia by different etiopathological processes, similar to the syndrome of mental retardation; and (3) specific symptom clusters within schizophrenia reflecting different disease processes that come together in different ways in different patients. Each of these models has strengths and weaknesses for the identification of etiology and pathophysiology.

Schwarz E, Bahn S., 2008. Cerebrospinal fluid: identification of diagnostic markers for schizophrenia. Expert Rev Mol Diagn. 8:209.

Schizophrenia is a complex neuropsychiatric disease but, despite extensive research efforts over the last 100 years, the etiology of this disorder remains elusive. Diagnosis is still based on a subjective, interview-based process, which may not align with the biological underpinnings of the symptoms. This old-fashioned descriptive approach contributes to the low treatment success and impedes early intervention, which is thought to be crucial for successful therapy. Therefore, there is an urgent need to discover biochemical analytes that facilitate an objective and reliable diagnosis. Disease markers might also have utility for tracking treatment success and compliance, as well as the discovery of novel drug targets. For schizophrenia and psychiatric disorders at large, analyzing cerebrospinal fluid (CSF) is an intuitive choice due to its close proximity to the brain and its clinical accessibility in the living patient. Although numerous studies have aimed to identify potential diagnostic markers in the CSF of schizophrenia patients, as yet not one has found its way to clinical application. Here, we review molecular alterations of proteins and metabolites that have been identified in schizophrenia CSF and discuss their potential applicability as diagnostic markers.